# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| 189 | | |
| International application No. | International filing date (*day/month/year*) | Priority Date (*day/month/year*) |
| PCT/KR 2003/001244 | 25 June 2003 (25.06.2003) | 26 June 2002 (26.06.2002) |

International Patent Classification (IPC) or national classification and IPC

IPC[7]: C07C 69/712, 67/31, C07D 263/58, 213/643, 241/18

Applicant

KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY

1. This international preliminary examination report has been prepared by this International Preliminary Examination Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I. ☒ Basis of the opinion
   - II. ☐ Priority
   - III. ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV. ☐ Lack of unity of invention
   - V. ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI. ☐ Certain documents cited
   - VII. ☐ Certain defects in the international application
   - VIII. ☒ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 19.01.2004 | 5 November 2004 (05.11.2004) |
| Name and mailing address of the IPEA/AT<br>Austrian Patent Office<br>Dresdner Straße 87<br>A-1200 Vienna<br>Facsimile No. 1/53424/200 | Authorized officer<br>MÜLLER-HIEL R.<br>Telephone No. 1/53424/434 |

Form PCT/IPEA/409 (cover sheet) (July 1998)

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/KR 2003/001244

## I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages 2, 3, 5-19, 21 , as originally filed
pages _____ , filed with the demand
pages 1, 4, 20 , filed with the letter of 23 September 2004 (23.09.2004).

☒ the claims:
pages _____ , as originally filed
pages _____ , as amended (together with any statement) under Article 19
pages _____ , filed with the demand
pages 22, 23 , filed with the letter of 23 September 2004 (23.09.2004).

☐ the drawings:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____.

☐ the sequence listing part of the description:
pages _____ , as originally filed
pages _____ , filed with the demand
pages _____ , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/ or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____.

☐ the claims, Nos. _____.

☐ the drawings, sheets/fig _____.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as „originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/KR 2003/001244

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-5 | YES |
| | Claims | ---- | NO |
| Inventive step (IS) | Claims | 1-5 | YES |
| | Claims | ---- | NO |
| Industrial applicability (IA) | Claims | 1-5 | YES |
| | Claims | ---- | NO |

Citations and explanations (Rule 70.7)

The following documents have been cited in the Search Report:

D1: GB 2038810 A
D2: JP 06247897 A2
D3: US 4531969 A
D4: US 4978774 A
D5: US 4550192 A
D6: DE 3409201 A
D7: EP 0157225 A
D8: EP 0062905 A

Document D1 (page 1, line 52 ff; claims 6-9) describes the esterification of a phenoxyphenol derivative (II) with the S-Isomer of a lactate derivative (III), wherein the leaving group X is preferably a methanesulfonyl group or a p-toluenesulfonyl group (page 2, line 22; claim 8). The reaction is carried out in the presence of a base, for example alkali metal carbonate (page 2, line 25), at a temperature range from 50 to 200°C (page 2, line 31; claim 9), in a suitable solvent, preferably a hydrocarbon, such as toluene or xylene (page 2, line 38), and yields the R-isomer of a phenoxyphenoxy propionic acid derivative (I). Continuous removal of water formed during the reaction is not mentioned in D1.
Accordingly, amended claims 1-5 of the application are acknowledged as novel over document D1.

Continuous removal of water formed during a reaction by azeotropic distillation is a routine method for a person skilled in the art. Nevertheless, this modification results in higher optical purities and yields, as mentioned in the description and explained in the letter from 23-9-2004. In the light of the teachings of D1, this result could not be anticipated. Therefore, an inventive step is acknowledged for amended claims 1-5.

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box V (page 1)

As indicated in the search report, documents D2-D8 merely describe the state of the art and are not considered of particular relevance concerning novelty and inventive step of the subject matter of the present application.

Industrial applicability is given.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/KR 2003/001244

**VIII. Certain observations on the international application**

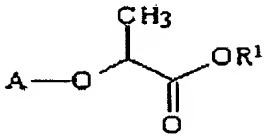
The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

New Claim 5 is a method claim characterized by the application of a certain apparatus. Such claims should be avoided. Instead, method claims should be characterized by process steps (eg. continous removal of water by azeotropic distillation). It is also noted, that an apparatus as mentioned in claim 5 and in the description is usually called "Dean-Stark trap".

# PROCESS FOR PREPARING (R)-ARYLOXYPROPIONIC ACID ESTER DERIVATIVES

## Technical Field

The present invention relates to a method for preparing optically active (R)-aryloxypropionic acid ester derivatives, and more particularly to a method for preparing (R)-aryloxypropionic acid ester derivatives represented by the following formula 1 with high optical purity and good yields at low cost via nulceophilic substitution reaction using phenol derivatives with various substituted functional groups and (S)-alkyl O-arylsulfonyl lactates as reactants in the presence of a proper solvent and a base at optimum temperature :



(1)

wherein $R^1$ is a $C_{1-6}$ -alkyl or benzyl group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenyloxyphenyl group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein the aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a $C_{1-4}$ -alkyl group, a $C_{1-4}$ -haloalkyl group, a $C_{1-4}$ -alkoxy group, and a $C_{1-4}$ -haloalkoxy group.

## Background Art

The compound represented by Formula 1, commonly called (R)-propionic

wherein $R^1$ is a $C_{1-6}$ -alkyl or benzyl group; $R^2$ is a $C_{1-6}$ -alkyl, phenyl group, or a phenyl group substituted with a $C_{1-6}$ -alkyl or a $C_{1-6}$ -alkoxy group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, a quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenyloxyphenyl group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein said aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a $C_{1-4}$ -alkyl group, a $C_{1-4}$ -haloalkyl group, a $C_{1-4}$ -alkoxy group, and a $C_{1-4}$ -haloalkoxy group.

Hereinafter, the present invention is described in more detail.

The present invention relates to a method for preparation of optically active (R)-propionic acid ester derivatives with high yield and good optical purity via nucleophilic substitution reaction using phenol derivatives and (S)-alkyl O-arylsulfonyl lactates as reactants, wherein the reactions are performed under a condition of solvent, temperature and leaving group, which are all specifically designed.

Phenol derivatives and (S)-alkyl O-arylsulfonyl lactates, reactants of the present invention as represented by the above Formulas 2 and 3, are known compounds and are synthesized by the known methods. For example, (6-chloro-2-benzoxazolyloxy)phenol can be prepared by a 4-step reaction using commercially available substances, such as aminophenol, urea, sulfuryl chloride, phosphorus pentachloride, and triethylamine, and solvents, such as xylene, acetic acid, chlorobenzene, and dichloroethane. And, (S)-alkyl O-arylsulfonyl lactate can be prepared by reacting (S)-alkyl lactate and arylsulfonyl chloride in the presence of triethylamine in dichloroethane solvent.

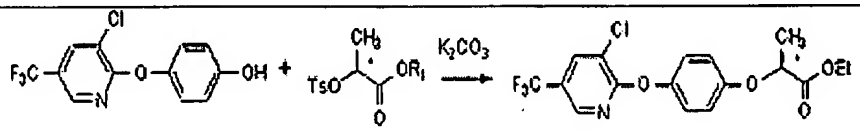
In the nucleophilic substitution reaction of the present invention, selection of

| | | | | | |
|---|---|---|---|---|---|
| ketone | | | | | |
| *Ratio of (R)/(S) isomers: Identified by LC | | | | | |

**Comparative Example 2**

The following Table 8 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(3-chloro-5-trifluoromthylpyridine-2-yloxy)phenoxy]propionate (compound 29) according to the known methods shown in the reaction scheme 2.

Table 8



| Reaction Solvent | Reaction Temperature | Reaction Time | Yield (%) | Ratio of (R)/(S) Isomers (%)* |
|---|---|---|---|---|
| Acetonitrile | Reflux | 5 hours | 72% | 95.0/5.0 |
| Methyl ethyl ketone | Reflux | 5 hours | 79% | 95.0/20.0 |
| Dimethylformamide | 80 ~ 90℃ | 4 hours | 70% | 93.0/7.0 |
| *Ratio of (R)/(S) isomers: Identified by LC | | | | |

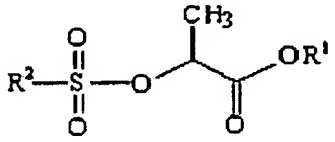
**Comparative Example 3**

The following Table 9 shows yields and ratio of optical isomers generated in the course of preparing (D+)-*n*-ethyl-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy]propionate (compound 32) according to the known methods shown in the reaction scheme 2.

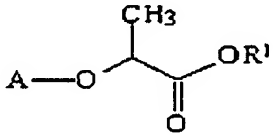
WHAT IS CLAIMED IS:

1. A method for preparing optically active (R)-aryloxypropionic acid ester derivatives represented by the following Formula 1 by reacting phenol derivatives represented by the following Formula 2 and (S)-alkyl O-arylsulfonyl lactate represented by the following Formula 3 in the presence of alkali metal carbonate in an aliphatic or aromatic hydrocarbon solvent under the temperature range of 60 to 100℃:


(2)




(3)




(1)

wherein $R^1$ is a $C_{1-6}$ -alkyl or benzyl group; $R^2$ is a $C_{1-6}$ -alkyl, phenyl group, or a phenyl group substituted with a $C_{1-6}$ -alkyl or a $C_{1-6}$ -alkoxy group; A is an aryl group selected from the group consisting of a phenyl group, a naphthyl group, a quinoxazolyloxyphenly group, a benzoxazolyloxyphenyl group, a benzothiazolyloxyphenyl group, a phenyloxyphenyl group, a pyridyloxyphenyl group and a pheyloxynaphthyl group, wherein said aryl group can be substituted with 1-3 functional groups selected from the group consisting of a hydrogen atom, a halogen atom, a nitro group, a nitrile group, an acetoxy group, a $C_{1-4}$ -alkyl group, a $C_{1-4}$ -haloalkyl group, a $C_{1-4}$ -alkoxy group, and a $C_{1-4}$ -haloalkoxy group.

2. In Claim 1, said hydrocarbon solvent is selected from the group consisting

of toluene, xylene, cyclopentane, cyclohexane, methylcyclohexane, cycloheptane, *n*-hexane, and *n*-heptane.

3. In Claim 1, said solvent is cyclohexane or xylene.

4. In Claim 1, said method for preparing optically active (R)-aryloxypropionic acid ester derivatives is performed using potassium carbonate as a base in cyclohexane as a solvent at 80℃.